PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WO/170	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/13946	International filing date *(day/month/year)* 09.12.2003	Priority date *(day/month/year)* 10.12.2002
International Patent Classification (IPC) or both national classification and IPC C07C69/612		
Applicant DOMPE S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.07.2004	18.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13946

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

2-5, 7-14, 16-20	as originally filed
1, 6, 15	filed with telefax on 12.01.2005

Claims, Numbers

1-7	filed with telefax on 12.01.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 8,9

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the opinion

1 In response to the written opinion the applicant has filed an amended set of claims and amended pages 1, 6, and 15 of the description.

1.1 On amended page 1 references to the documents **D18** and **D19** have been introduced. Furthermore, on amended pages 6 and 15 the name (R)(-)-dimethyl 3-(4-isobutyl)-2-oxobutan-1-phosphonate has been corrected, based on the name of example 6 on page 14, line 14, to read now (R)(-)-dimethyl 3-(4-isobutylphenyl)-2-oxobutan-1-phosphonate. These amendments, in principle, would comply with the requirements of Articles 19(2) and 34(2)(b) PCT. However, the amended pages do not fit within the text of the application documents on file: On amended page 1, the formula (II) and the text of lines 21-22 of original page 1 are missing. On amended page 6, the text of lines 1-8 is identical with the text of original page 5, lines 16-23, and the text of original page 6, lines 25-32, is missing on the amended sheet. Similarly, the text of amended page 15, lines 1-9 is identical with the text of original page 14, lines 23-31, and the text of original page 15, lines 24-32, is missing on amended page 15.

1.2 Amended claim 1 appears to be based on the original claims 5 and 6 and the definition of (Ar)aryl according to page 2, lines 1-13, of the description. However, no basis can be found in the application as filed for the Ar value "4-(1-oxo-2-isoindolinyl)-phenyl" (cf. original page 2, line 9: 1-oxo-2-isoindolinyl-phenyl) and the Ra/Rb value "-X-$(CH_2)_n$-Z" (cf. original claim 5 and original page 1: di-X-$(CH_2)_n$-Z). Similarly, no basis can be found in the application as filed for the preferred (Ar)aryl values "5-benzoyl-phenyl" and "2-acetoxy-phenyl" in amended claim 2 (cf. original page 2, lines 7-10). Therefore, amended claims 1 and 2 extend beyond the scope of the application as filed and do not comply with the requirements of Articles 19(2) and 34(2)(b) PCT.

Therefore, this report has been established as if the said amendments had not been made. The remaining amendments appear to comply with the Articles 19(2) and 34(2)(b) PCT.

2 The application is now directed to

(i) the second medical use of arylethylketones of formula (I) (claims 1-3, 5, 7),

(ii) the second medical use of certain specific examples (claims 4 and 7), and
(iii) a pharmaceutical composition comprising the compounds of claims 1-5 (claim 6).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The application does not comply with the requirements of Article 6 PCT for the following reasons.

1.1 Second medical use claims 1-5 are not acceptable under Article 6 PCT, because the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition/disease. The objection could be overcome by either introducing in the claims a list of pathological conditions/diseases cited in the application or in claim 7, or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.

1.2 The vague non-limiting definition of aryl in the description as the "aryl portion of known anti-inflammatory 2-aryl-propionic acids such as ..." (page 2, lines 4-6) implies that the scope for which protection is sought may be different from what is defined in claims. This inconsistency between the description and the claims renders the claims unclear.

1.3 The Ra/Rb value "di-X-$(CH_2)_n$-Z" in original claims 1 and 5 is incomprehensible due to the prefix "di". It is noted that this objection cannot be overcome by the deletion of the prefix "di" (cf. Articles 19(2) and 34(2)(b) PCT).

2 Reference is made to the following documents.

D1: Beilstein, BRN's 1942753, 1943166, 1943612, 1943613, 1945434, 1945435, 1945436, 1945437, 1948204, 1950022, 1968443, 2362885, 2447357, 2451750.
D2: Beilstein, BRN's 1955069, 1958359.
D3: Beilstein, BRN's 2104506, 2451415.
D4: Beilstein, BRN 3242777.

D5: Beilstein, BRN 2842765.
D6: Beilstein, BRN's 3033411, 3651979, 3651980.
D7: Beilstein, BRN 4661814.
D8: Beilstein, BRN 5013506.
D9: Beilstein, BRN's 5379213, 5379214.
D10: Beilstein, BRN 6863126.
D11: Beilstein, BRN 6978265.
D12: Beilstein, BRN 7020327.
D13: Beilstein, BRN 4981202.
D14: Beilstein, BRN's 3292936, 8911430, 8911858, 8912139, 8912482.
D15: Beilstein, BRN 5535609.
D16: JP 05 286902 A, 02.11.1993.
D17: Beilstein, BRN 6727608; & Farmaco Ed. Sci. **1981**, *36*, 1037-1056.
D18: WO 00/24710 A, 04.05.2000.
D19: WO 01/58852 A, 16.08.2001.

3 Novelty

D1 to **D16** disclose already compounds (I) but do not refer to any therapeutic application or pharmaceutical compositions comprising such compounds (I). These documents appear thus not relevant to the question of novelty of the current set of claims.

D17 relates to the antiinflammatory properties of phenyl-indazoles such as the ketone (XXV). The present claimed matter appears novel vis-à-vis **D17**, because the (Ar)phenyl group of the present compounds (I) is not substituted with an indazolyl moiety, contrary to the compounds of **D17**.

D18 and **D19** relate to the inhibition of the interleukin 8 (IL-8) induced chemotaxis of neutrophils by ketoprofen PhCOPh-CH(CH_3)-COOH (**D18**), aryl-propionyl-sulfonamides Ar-CH(CH_3)-C(O)-NR'-SO_2R (**D18**), and aryl-propionyl-amides Ar-CH(CH_3)-C(O)-NRR' (**D19**). The present compounds (I) differ from those of **D18** and **D19** in as far as they represent ketones rather than propionic acid derivatives. The present claimed matter is thus novel vis-à-vis **D18** and **D19**.

The application appears thus to comply with the criterion of novelty according to Article 33(2) PCT.

4 Inventive Step

4.1 The application describes the synthesis of certain compounds (I) and reports that three R-enantiomers of such compounds (I) inhibit the chemotaxis of human neutrophils stimulated by IL-8 (the application, page 7, lines 22-27; and page 9). The compounds (I) are thus expected to be useful in the treatment of neutrophil-dependent inflammatory diseases such as psoriasis, rheumatoid arthritis and others (page 9, line 29 to page 10, line 8).

4.2 **D18** explains the contributions of the R- and S-enantiomers of ketoprofen PhCOPh-$CH(CH_3)$-COOH to the antiinflammatory activity of the racemate and their role in cytokines modulation. In this context it is stated that both enantiomers exhibit an inhibitory effect on the neutrophil response to IL-8. However, the R-enantiomer compared with the S-enantiomer has a lower potency as cyclooxy-genase inhibitor and therefore a lower inhibition activity on the synthesis of PG which, in their turn, exert an inhibitory and controlling action on the release of cytokines which contribute to amplify the proinflammatory effects of neutrophils. As a consequence, the S-enantiomer is less (and thus the R-enantiomer is more) effective in the treatment of neutrophil-dependent inflammatory conditions such as psoriasis and others (cf. **D18**, page 4, line 33 to page 5, line 32). Based on this background knowledge the authors of **D18** have developed further anti-inflammatory propionic acid derivatives Ar-$CH(CH_3)$-C(O)-NR'-SO_2R that inhibit the neutrophil response to IL-8.

The present compounds (I) differ from ketoprofen PhCOPh-$CH(CH_3)$-COOH mentioned in **D18** in being ketones Ar-$CH(CH_3)$-C(O)-CHRaRb rather than propionic acid derivatives. Starting from **D18** as most relevant state of the art, the problem underlying the present application may be seen in the provision of further antiinflammatory compounds that inhibit the chemotaxis of neutrophils.

D17, furthermore, relates to antiinflammatory phenyl-indazoles such as the propionic acid Indazolyl-Phenyl-$CH(CH_3)$-COOH (IV) and the ketone Indazolyl-Phenyl-$CH(CH_3)$-CO-CH_3 (XXV), which are structurally related to ketoprofen, mentioned in **D18**, as well as to the present compounds (I). Hence, it appears obvious that the skilled person wishing to provide further compounds of the desired activity, would consider to replace the propionic acid side chain of ketoprofen mentioned in **D18** or of similar known NSAID's (such as ibuprofen etc.) with the side chain of the antiinflammatory ketone (XXV) of **D17** and, thereby arrive at the present compounds (I). In the

absence of any substantiated unexpected effect(s) of the present compounds (I) in comparison with the closest related compound(s) of **D18** (e.g. the present (R)-(–)-3-[(3'-benzoyl)phenyl]butan-2-one (page 6, line 22) in comparison with R-ketoprofen mentioned in **D18**), no inventive activity would be seen the claimed matter.

Consequently the claims 1-9 do, at present, not meet the requirements of Article 33(3) PCT.

5 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in **D17** is not mentioned in the description, nor is this document identified therein.

"CHIRAL ARYLKETONES IN THE TREATMENT OF NEUTROPHIL-DEPENDENT INFLAMMATORY DISEASES"

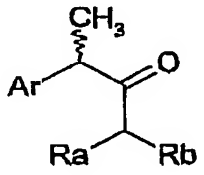
The present invention relates to chiral arylketones, a process for their preparation, and pharmaceutical compositions containing them, which are useful in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleate neutrophils in the inflammatory sites.

Other classes of compounds, such as R-2-arylpropionic acid amides and N-acylsulfonamides useful in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleate neutrophils in the inflammatory sites, have been described in WO 01/58852 and WO 00/24710 respectively.

The compounds of the invention are generally known compounds and disclosed in Belstein Handbook of Organic Chemistry.

Detailed description of the invention

More specifically, the present invention relates to chiral arylketones of general formula I:



(I)

wherein:

Ar is an aryl group;

Ra and Rb are independently chosen in the group of hydrogen, linear or branched C_1-C_6 alkyl, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_1-C_4-alkylphenyl, C_1-C_4-alkyl(α-or β-naphthyl), C_1-C_4-alkyl(2, 3, 4-pyridyl), cyano (-CN), carboxyamide, carboxyl or carboxyesters of formula CO_2R'' wherein R" is the residue of a linear or branched C_1-C_6 aliphatic alcohol, a phosphonate $PO(OR'')_2$ wherein R" is as defined above, a group of formula di-X-$(CH_2)_n$-Z, wherein X is a CO, SO, SO_2 group; Z is H, *tert*-butyl, isopropyl, CO_2R'', CN, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_3-C_6 cycloalkyl, NH-BOC, NH_2;

n is zero or an integer from 1 to 3; or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-1, 3-dioxanyl-2, 2-disubstituted of formula II:

which are known compounds and can be obtained from the individual racemates using known methods of optical resolution.

The preparation of the carbanions of formula V consists in a process of C-acylation in virtually neutral conditions, fully described in the literature (see, for example, D. W. Brooks *et al.*, Angew. Chem. Int. Ed. Engl., 18, 72, 1979), as well as monoesters of malonic acids and of monosubstituted malonic acids, also on sulfinylacetic acids, sulfonylacetic acids and phosphonoacetic acids. All these acids are known in the literature or can be prepared using known methods, such as monosaponification of diesters of malonic acids and their monosubstituted analogues or saponification of phosphonoacetic acids and 2-substituted analogues; sulfinylacetic and sulfonylacetic acids may be obtained by oxidation of ethers of thioglycolic acid. Alternatively, it is possible to use lithium enolates of formula V, obtained by reaction of lithium alkyls with known alkyl esters of alkylphosphonates (see, for example, N. Mongelli *et al.*, Synthesis, 310, 1988) or with esters of acetic acid (according to D.H. Harris *et al.*, Tetrah. Lett., 28, 2837, 1987).

For the preparation of enolates of formula Va, and more generally for the procedure of acylation of the cyclic alkylidenesters of malonic acid (also known as Meldrum acids) with the activated species of a carboxyl of formula IV, the method described by Y. Oikawa *et al.*, J. Org. Chem., 43, 2087 (1978), R.P. Houghton and D.J. Lapham, Synthesis 451 (1982) and C.C. Chan and X. Hung, *ibidem*, 452 (1982) is used.

The preparation of dialkoxyphosphonoacetic acids and that of their esters are exemplified in US 4151172 (April 24, 1979), or described by R.A. Malevannaya *et al.*, in Zh. Obshch. Khim. 41, 1426 (1971).

Specific examples of the compounds of the invention are:

methyl (R)(−)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

methyl (S)(+)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

(R,S) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid;

methyl (R)(−)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(R)(−)-3-[(4'-isobutyl)phenyl]butan-2-one;

(S)(+)-3-[(4'-isobutyl)phenyl]butan-2-one;

(R)(−)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(−)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate;

(S)(±)-dimethyl 3-(3'-phenoxy-phenyl)-2-oxo-butyl-1-phosphonate;

In an inert-gas atmosphere, a solution of butyl lithium (1.56 M; 13.3 mL, 0.027 mol) in hexane is added dropwise to a solution of dimethyl methylphosphonate (3.69 g; 0.03 mol) in anhydrous THF (10 mL) cooled to −70°C. The mixture is stirred for 15 min before addition, dropwise, of a solution in anhydrous THF (10 mL) of methyl ester or of imidazolide, prepared as previously described.

Upon completion of the dripping step, the reaction mixture is kept, under stirring, for 1 h at −70°C and then for 1 h at room temperature. The mixture is then cooled to −10°C, and 1.8 mL of glacial acetic acid is added dropwise. The solvent is removed under vacuum, the residue is diluted with water, and the mixture is repeatedly extracted with dichloromethane (4x50 mL). The organic extracts are dried on sodium sulfate; after evaporation of the solvent, the residue is purified on silica gel, eluted with AcOEt to yield, as a colourless oil, 3. 02 g of (R) (−)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate.

$[\alpha]_D$ = −171° (c=1; CH_3OH); ^{1}H-NMR ($CDCl_3$): δ 7.03 (s, 4H); 4.1-3.9 (dd, 2H, J_1=15Hz, J_2=8Hz); 3.8 (s, 3H); 3.70 (m, 1H); 3.65 (s, 3H); 2.55 (d, 2H, J=8Hz); 1.75 (m, 1H); 1.50 (d, 3H, J=8Hz); 0.85 (d, 6H, J=7Hz).

Example 7

(R) (−) 2-(4-isobutylphenyl)-7-*tert*-butoxycarbonylamino-heptan-3-one.

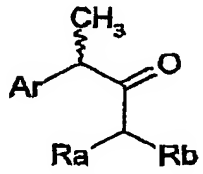
A solution of ethyl 5-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-pentanoate (WO 94/10127) (1.59 g) in 3 mL of methanol is added to 8 mL of a 0.63 N solution of $LiOH.H_2O$ in water/methanol (1:1); the mixture is stirred for 12 h at room temperature. The mixture is diluted with 10 mL of a saturated solution of monosodium phosphate, and the excess of methanol is removed under vacuum. The mixture is extracted with ethyl acetate (2x10 mL); from the organic extracts, combined and dried on sodium sulfate, by evaporation of the solvent 1,4 g (4.8 mmol) of 5-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-pentanoic acid are obtained.

To a solution of the acid (2.4 mmol) in 8 mL of anhydrous THF 0.27 g (2.4 mmol) of commercially available magnesium ethylate is then added, and the suspension is stirred at room temperature up to complete dissolution of the reagents to form the magnesium complex.

Then a solution of 0.3 g of (R) (−) 2-(4'-isobutylphenyl)-propionylimidazolide is added, and the mixture is stirred for 4 h at room temperature. The mixture is acidified by addition of a few mL of 50% aqueous AcOH, and the solvent is evaporated under vacuum. The

CLAIMS

1. Use of (*R,S*)-1-Arylethylketone compounds of formula I and their single (*R*) and (*S*) enantiomers:



(I)

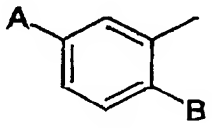
wherein:

- Ar represents phenyl, optionally substituted by one to three substituents, which are the same or different from one another, selected from:

halogens, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halogen-C_1-C_3-alkyl, halogen C_1-C_3-alkoxy, benzoyl;

or Ar represents 4-thienoyl-phenyl, 4-(1-oxo-2-isoindolinyl)-phenyl, 3-chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl, 6-methoxy-β-naphthyl, 1-hydroxy-phenyl-1-methyl;

or Ar represents a residue of formula III:

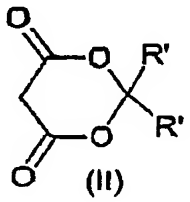


(III)

wherein A is benzyl, phenoxy, benzoyl, benzoyloxime, 1-hydroxy-phenyl-1-methyl, B is hydroxy, C_1-C_4-acyloxy or a group of formula -O-C(=S)-N$(CH_3)_2$, or -S-C(=O)-N$(CH_3)_2$;

- Ra and Rb are independently chosen in the group of hydrogen, linear or branched C_1-C_6 alkyl, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_1-C_4-alkylphenyl, C_1-C_4-alkyl(α-or β-naphthyl), C_1-C_4-alkyl(2, 3, 4-pyridyl), cyano (-CN), carboxyamide, carboxyl or carboxyesters of formula CO_2R'' wherein R'' is the residue of a linear or

branched C_1-C_6 aliphatic alcohol, a phosphonate $PO(OR")_2$ wherein R" is as defined above, a group of formula $-X-(CH_2)_n-Z$, wherein X is a CO, SO, SO_2 group; Z is H, *tert*-butyl, isopropyl, $CO_2R"$, CN, phenyl, α-or β-naphthyl, 2, 3, 4-pyridyl, C_3-C_6 cycloalkyl, NH-BOC, NH_2; n is zero or an integer from 1 to 3; or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-1, 3-dioxanyl-2, 2-disubstituted of formula II:



(II)

wherein R' is methyl or ethyl, or the two groups R' form a cyclohexane or cyclopentane ring,

in the preparation of a medicament for the treatment of diseases that involve IL-8 induced human PMNs chemotaxis.

2. Use of compounds according to claim 1 wherein Ar represents a residue 4-isobutyl-phenyl, 3-benzoyl-phenyl, 5-benzoyl-phenyl, 2-acetoxy-phenyl, 3-phenoxy-phenyl.

3. Use of compounds according to claims 1 or 2 selected from:

methyl (R)(−)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;
methyl (S)(+)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;
(R,S) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid;
methyl (R)(−)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;
(R)(−)-3-[(4'-isobutyl)phenyl]butan-2-one;
(S)(+)-3-[(4'-isobutyl)phenyl]butan-2-one;
(R)(−)-3-[(3'-benzoyl)phenyl]butan-2-one;
(R)(−)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate;
(S)(±)-dimethyl 3-(3'-phenoxy-phenyl)-2-oxo-butyl-1-phosphonate;
(R)(−)-2-(4-isobutylphenyl)-pentan-3-one;
(S) (+) ethyl-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;
(S) (+)-3-[(3'-benzoyl)phenyl]butan-2-one;
(R)(−)-2-(4-isobutylphenyl)-4-phenyl-butan-3-one;

(R)(–)-2-(4-isobutylphenyl)-5-phenyl-pentan-3-one;
(R)(–)-2-(4-isobutylphenyl)-5-(pyrid-3-yl)-pentan-3-one;
(R,S) 5-(4'-isobutylphenyl)-hexan-2, 4-dione;
(R,S) 1-phenyl-5-(4'-isobutylphenyl)-2, 4-hexandione;
(R,S) 1-(pyrid-2-yl)-4-(4'-isobutylphenyl)-1, 3-pentadione;
(R) (–) 2-(4-isobutylphenyl)-7-*tert*-butoxycarbonylamino-heptan-3-one;
(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfoxide;
(R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfoxide;
(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfone;
(R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfone;
(R,S) 2-(3'-phenoxyphenyl)-3-oxo-butyl, methyl-sulfone;
(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, phenyl-sulfone;
(R)(-)-4-(4'-pyridyl)-2-[(4"-isobutyl)phenyl]butan-3-one;
(R) (+)-5-[2-(4-isobutyl-phenyl)-propion-l-yl]-2, 2-dimethyl-1,3-dioxan-4, 6-dione;
(R) (–)-5-[2-(3'-benzoyl-phenyl)-propion-l-yl]-2, 2-dimethyl-1,3-dioxan-4, 6-dione.
(R)-2-[4-(1-oxo-2-isoindolinyl)phenyl]-3-oxo-valeramide;
(R)-2-[4-(1-oxo-2-isoindolinyl)phenyl]-3-oxo-valeronitrile;

4. Use of compounds:
(R)(-) methyl 4-[(4'-benzoyloxy)phenyl]-3-oxopentanoate,
(R)(-) methyl-4-[(4'-isopropylsulfonyloxy)phenyl]-3-oxopentanoate and
(R)(-) methyl-4-{[4'-(2"-ethyl)phenylsulfonylamino]phenyl}-3-oxopentanoate,
in the preparation of a medicament for the treatment of diseases that involve IL-8 induced human PMNs chemotaxis.

5. Use of compounds according to Claims 1 or 2, wherein the steric configuration of the carbon atom to which the residue Ar is bound corresponds to the enantiomer (*R*).

6. Pharmaceutical compositions containing a compound according to any one of Claims 1 to 5 in admixture with a suitable carrier thereof.

7. Use of the compounds according to any one of Claims 1 to 5 in the preparation of medicaments for the treatment psoriasis, rheumatoid arthritis, ulcerative cholitis, acute respiratory distress syndrome (ARDS), idiopathic fibrosis,

glomerulonephritis, bollous pemphigo and for the prevention and the treatment of damages caused by ischemia and reperfusion.